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HIGHLIGHTS

Phytochemicals: Do they belong on our plate for sustaining healthspan?

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Abstract
That phytochemicals are a critical part of enhancing healthspan is in our minds a linchpin of responsible public health messaging, yet, recent dietary guidelines and strategies for implementing precision nutrition largely ignore roles of phytochemicals. Epidemiological evidence points strongly to beneficial effects of phytochemical-rich foods on the prevention of essentially all chronic diseases. An extraordinary multitude of phytochemicals have been shown in preclinical settings to be potent allies in our fight against the entire spectrum of chronic diseases and many acute conditions such as infections. Yet unequivocal proof of this concept is problematic due to the nature of the clinical trials that must be part of such a proof. More rigor in the design and implementation of such trials is essential. Artificial intelligence, machine learning, metabolomics, microbiomics, proteomics, and other high-powered data processing modalities, may inform the phyto-dynamic actions on very specific metabolic pathways. As phytochemical abundance appears to be declining in our food supply, the need for better and more strategically focused science is great.

KEYWORDS
clinical trial, dietary supplement, food, nutrition, sulforaphane

The nutritional establishment has long paid close attention to the macronutrient, fiber, vitamin, and mineral content of our foods. Great strides have been made in the understanding of a wide variety of nutritional requirements, the interplay between metabolic pathways, the complexities associated with calorie delivery, satiety and regulatory hormones, and the effects that diet can have on triggering a panoply of inflammation-, immune-, energy-, sleep-, and neurological complications. There has been spectacular progress over the last century vis-a-vis discovery of essential vitamins and minerals and an understanding of what they do and why they are critical. The partial deciphering of the gut microbiome over the past two decades has launched an incredible ongoing investigation of the interplay of human nutrition with that of our microbial symbionts, along with how that impacts immunity, chronic disease, and healthspan. Yet in that same two decades, much of the wisdom of early predictions that phytochemicals are essential to our healthspan has been marginalized and most assuredly has not been used to best advantage. To wit, 23 years ago, the former president of the International Union of Nutrition Sciences, Mark Wahlqvist, presciently proposed that "The phytochemical adequacy of the diet can be assessed to some extent by the food variety score," and that "Food selection for phytochemical intake will need to take account of a number of potential sources of such compounds" (Wahlqvist, Wattanapenpaiboon, Kouris-Blazos, Mohandoss, & Savige, 1998).

Phytochemicals are most simply defined as chemicals, compounds, or agents that are present in plants at very low levels compared to the proteins, carbohydrates, fats, and fiber that make up the bulk of their matter. Phytochemicals are products of secondary metabolism—in other words, they contribute to the plants' protection or give them an advantage in the environment in which they live, but are not an integral part of their energy generating, growing, and replicating machinery. These 50,000 or more compounds have recently been described as the dark matter of nutrition, and are said to be "largely invisible to both epidemiological studies, as well as to the public at large" (Barabási, Menischetti, & Loscalzo, 2020). They include colors (pigments), scents, and various compounds with antibiotic or other defensive activities.

The major agencies responsible for funding and thereby direction setting of nutrition research in the United States (the NIH and the USDA) have either sidestepped or ignored bringing phytochemical research into the clinic in a meaningful way. The USDA in the United States, being at the nexus of food, agriculture, horticulture, nutrition (plant and animal) research, has, to its credit, begun to create specific, public phytochemical data sets for glucosinolates, flavonoids, proanthocyanidins, and isoflavones. However, neither the word *phytochemical* nor concepts related to plant-based secondary products (or "compounds") are used at all in the 164 pages of the recently published "Dietary Guidelines for Americans 2020 to 2025" (USDA, 2020), nor many other high-profile comprehensive treatises on food and nutrition published recently (Fanzo et al., 2020; Wallace et al., 2020; Willett et al., 2019). This lack of meaningful focused attention on phytochemicals is also reflected in the over 100 page "Advancing Nutrition and Food Science: 80th Anniversary of the Food and Nutrition Board" (NASEM, 2020), wherein some of the many achievements in nutrition research are rightly touted, but there is no mention of phytochemicals. The NIH has recently presented a strategic plan for "precision nutrition" to define individualized diets across the lifespan by optimizing discovery science across many disciplines (NIH, 2020). Whilst *phytochemicals* are not mentioned per se, a listed objective is to identify nutrition dark matter that appear directly after eating food or in response to metabolism by the host and microbiota—and to understand their functions. The last element is critical.

That phytochemicals are a critical part of enhancing healthspan is in our minds a linchpin of responsible public health messaging, yet unequivocal proof of this concept is problematic due to the nature of

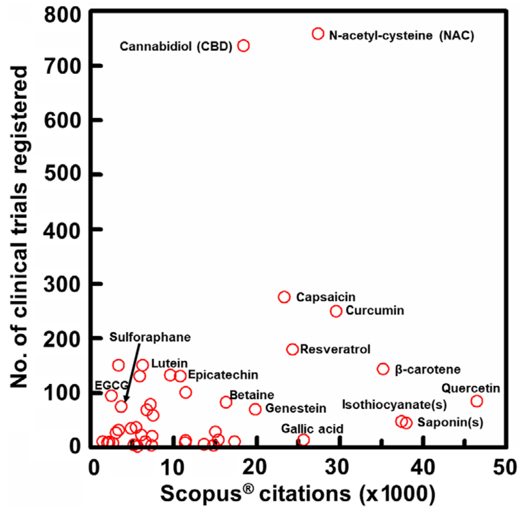

FIGURE 1 Clinical versus overall research attention to specific phytochemicals as determined by number of clinical trials registered on clinicaltrials.gov and number of raw citations on the database Scopus® (assessed February 2021)

the clinical trials that must be part of such a proof. Nutritional epidemiological evidence points strongly to beneficial effects of foods rich in phytochemicals in general on the prevention of essentially all chronic diseases, and thus on enhancing healthspan. There is an extraordinary multitude of phytochemicals whose chemistry is well described and that have been shown in preclinical settings to be potent allies in our fight against the entire spectrum of chronic diseases as well as many acute conditions such as infections. The list is far too long to discuss in its entirety but we present a small snapshot of some of the more well-studied (presumptively beneficial) phytochemicals (Figure 1). In the context of this conversation, it is of the utmost importance to remember that these phytochemicals come from edible plants, and that the human species has evolved eating them.

Unfortunately, publication density does not presage extent of clinical evaluation of efficacy. Also shown in Figure 1 are the numbers of clinical trials listed in ClinicalTrials.gov for these compounds. Many trials may have never enrolled participants, nor achieved study endpoints or published results. Thus, any association of numerology with clinical efficacy is improbable. Our colleague Yang (2020) very recently lamented the difficulties in clinical studies of phytochemicals in a *Highlight* in the fourth issue of this journal. We have had extensive experience with a particular family of phytochemicals—the glucosinolates and isothiocyanates otherwise known as mustard oils (Yagishita, Fahey, Dinkova-Kostova, & Kensler, 2019), and have expressed strong opinions about ongoing research strategies utilizing them (Fahey & Kensler, 2021).

Establishing rigorous evidence of benefit of phytochemicals on health is fraught with challenges in the settings of clinical trials. Even in meticulously designed and executed trials, results can be ambiguous. For certain, translation of research findings through the bidirectional loop of field—bench—clinic—diet must assess best approaches to preventive interventions, regardless of the nature of the presumed bioactive constituents. Issues of standardization and validation of plant sources used in clinical trials with foods, herbal medicines, nutraceuticals, or dietary supplements are paramount. Reproducible documentation and delivery of standardized foods and their derivatives (e.g., plant extracts, supplements) are critical to the clinical testing of foods for enhanced healthspan to allow for others to replicate the dosing regimen and deliver the same amount of the phytochemical(s) of interest within a reasonably similar plant matrix. Knowledge of the following plant-related factors are required: (1) genetics or pedigree; (2) environment or provenance; and (3) contamination, both deliberate (fraudulent identification of plant species) and accidental (excessive trace elements, pesticides, microbes). The issues associated with scientific development of medicines from plants have been summarized in a historical context by the Talalays (Talalay and Talalay, 2001), and pragmatically by us (Fahey & Kensler, 2021) and by others (Diedrich, 2020; Newman & Cragg, 2016). Such practices have not been uniformly applied to the clinical study of phytochemicals to date, even as relates to the measurement of the quantity of a particular phytochemical within the foodstuff. Optimization of agent/plant pharmacology is facilitated by knowledge of one or more of the molecular targets of the phytochemical(s) of interest to provide pharmacodynamic biomarkers reflecting bioavailability (internal dose), schedule effects, and durability of responses (Yagishita, Gatbonton-Schwager, McCallum, & Kensler, 2020).

A major impediment to rigorous evaluation of phytochemicals for improved healthspan may lie in the absence of focused development strategies. As an example, we recently reviewed the use of pharmacodynamic biomarkers in the development of three agents targeting the transcription factor NRF2 (Yagishita et al., 2020). Two were developed by Pharma: (1) the rapid repositioning of dimethyl fumarate (Tecfidera) for the treatment of relapse-remitting multiple sclerosis leading to FDA approval in 2012 and (2) the *de novo* development of bardoxolone methyl for treatment of chronic kidney disease now in several Phase III trials. Bardoxolone methyl, first synthesized from a natural product backbone in 1998, has been used in just five clinical trials since 2011 and yet is likely near NDA registration with the FDA. The third agent is the phytochemical sulforaphane. As presented in Figure 1, there have been ~3700 publications featuring sulforaphane and 75 clinical trials (mostly Phase I) listed on ClinicalTrials.gov. NIH rePORTER lists 653 annual funded grants using sulforaphane since 1997 to present—to the tune of almost $245 M total funding (https://reporter.nih.gov/search/vceUuufIKkiUcX7nPStX9A/projects). While sulforaphane certainly remains a phytochemical of interest for disease prevention (and therapy), no definitive clinical trial results support its consumption for preservation of healthspan as yet. Is this a function of frank lack of efficacy, current precepts of peer review (focused on mechanisms more than translation), or a completely fragmented, somewhat siloed approach to agent development by individually funded investigators? For certain, if reductionist, single-agent approaches to phytochemical evaluation are to succeed, more efficient paradigms are needed for their implementation to practice.

Could dietary supplement formulations carry us forward? It should be noted that more than three quarters of all Americans now take supplements, and 10% of us take four or more such supplements (CRN, 2019). It is thus not heretical to assume that well-crafted supplements might- and could be part of the solution, should the science support such a strategy. It is important to note, however, that despite encouragement from epidemiological studies targeting nutrients, evidence to date from randomized clinical trials with mineral or vitamin supplements does not support efficacy for reduction of cancer risk (Bjelakovic, Nikolova, Gluud, Simonetti, & Gluud, 2007; Guallar, Stranges, Mulrow, Appel, & Miller, 2013). Furthermore, accumulating evidence from microbiome studies over the past decade or so underscores the tremendous importance of the fiber (a.k.a. prebiotic) component of unprocessed or lightly processed plant foods (Monteiro et al., 2017, 2019) in the maintenance of a healthy gut. Many complex plant carbohydrates and fibers are not substrates for mammalian enzymatic hydrolysis, rather, they are utilized by very specific consortia of both allochthanous and autochthanous intestinal microbes to produce short-chain fatty acids (acetate, butyrate, and propionate) that are essential not only to gut health but to a range of metabolic pathways critical to healthspan in general (Mamic, Chaikijurajai, & Tang, 2021). When phytochemicals are isolated from their fibrous matrix (the plant), and people start depending too heavily on supplementation with isolated compounds, the loss of that fiber is far more than just window dressing and a "vehicle" in which to convey the phytochemical, and it has far-reaching effects on health.

Whereas climate change threatens our food security, a phytochemical climate change is upon us. Phytochemical abundance (see Barabási et al., 2020) appears to be declining in our food supply (Figure 2). This is due to multiple overlapping reasons, all of which too can and should be debated and better understood. ***First***. In modern times, the process of plant breeding and selection has focused almost exclusively on yield (kilograms per hectare) and on disease resistance and adaptability to particular climates. Thus, the minor components (e.g., phytochemicals) are neglected in favor of carbohydrates proteins and fats. Once yield and disease resistance are taken care of, then the target is the seduction of our sense of taste—accomplished primarily with sugar, fat, and salt (Katz, 2018; Schatzker, 2015). In the case of fruits and vegetables, that frequently translates into reduced bitterness (e.g., reduction of specific phytochemicals, many of which may be beneficial) and more sweetness (e.g., sugars). Although this taste objective is not always a target in fruit and vegetable breeding, it is almost always a consequence. It results in a diminished sensory experience, and thus, we argue, in a reduced benefit to healthspan. ***Second***. Modern agriculture and horticulture have overwhelmingly favored monoculture and the abundant application of synthetic herbicides, insecticides growth promoters and hormones (yes, this happens to plants too—not just livestock), microbicides, desiccants, waxes, dyes, and preservatives. These are antithetical to the development of a healthy soil/plant microbiome and to the natural development of a complex phytochemical milieu. ***Third***. Edible plant genetic diversity has plummeted in the last century (Siebert & Richardson, 2011). Thus, in addition to the widely recognized decline in the diversity and number of species in the wild, the number of heirloom varieties and "cultivars" of essentially every herb, fruit, and vegetable in common use has plummeted. That loss of within-species diversity has almost certainly had concomitant reductions in

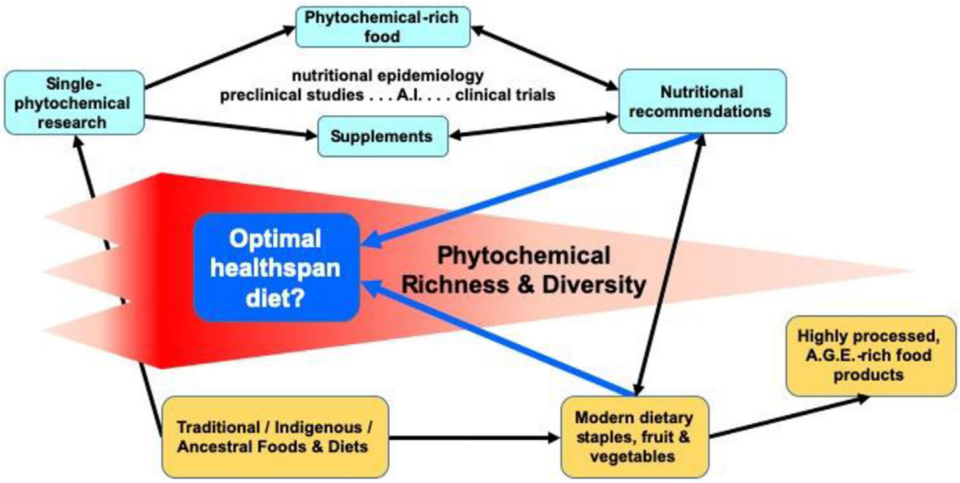

FIGURE 2 Phytochemical richness and diversity in the food supply. The central red triangle can more or less be viewed as a time continuum. The smaller red triangles pointing to the left remind us that most phytochemicals isolated for research have their origins in ancestral foods, not in today's highly processed food-like substances

phytochemical availability to the consumers of those foods. Perhaps one of the more ominous sequelae of this reduced diversity on the food interactome is captured in recent work showing that the most important predictor of gut microbiome health (e.g., its diversity) is the diversity of plants consumed, as opposed to the quantity (McDonald et al., 2018).

Nowadays, with the advent of artificial intelligence (A.I.), machine learning, metabolomics, microbiomics, proteomics, and other high-powered data processing modalities, we can see the impact that these widely diverse phytochemicals have on very specific metabolic pathways as outlined in this journal (e.g., Stoner, 2020; Wolfender, Queiroz, & Allard, 2020) and elsewhere (Allard et al., 2018; Chae, Kim, Nilo-Poyanco, & Rhee, 2014; Laponogov et al., 2021; McDonald et al., 2018). It can thereby be inferred, or is readily apparent, precisely which chronic disease conditions these pathways impact. This approach has already been applied elegantly with a variety of chronic conditions (Axelsson et al., 2017; Barabási et al., 2020; Ho et al., 2018), but the uphill climb is still steep. We know from our work with broccoli sprouts that much of that work highlighting specific phytochemical-wellness pathways also correlates extraordinary well with nutritional epidemiologic research where that research exists. Correlating observational epidemiologic research with causation, always rife with controversy, is especially so when the data dimensionality or number of layers of outcome observations balloon, as they do when combining genomic biobanking with a number of the "-omics." Here too, though, A.I. and machine learning is facilitating building such predictive models (Narita, Ueki, & Tamiya, 2021).

Returning to the question posed in the title of this short commentary: Do phytochemicals belong on our plate for sustaining healthspan? We believe that the evidence points to their necessity in the context of living a long life free of chronic diseases. Yet sadly, the evidence is still so poorly dispersed across the spectrum of 50,000+ phytochemicals that it is as of yet impossible to cite irrefutable human clinical interventions to support this statement. We have provided an assessment of some of the reasons for this and some of the problems in developing such conclusive proof. We have also indicated where we think the future is headed. Western consumers appear fixated on increasing their vitamin, mineral, and supplement intake, but a clear-eyed look at what has happened to diet and nutrition over the past two decades, two generations, or two centuries, cannot help but bring one to conclude that a return to a more phytochemical-rich and phytochemically diverse diet ought to be guiding us to sustained good health.

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DATA AVAILABILITY STATEMENT

The datasets analyzed for this review are found in the cited, published literature.

AUTHORS' CONTRIBUTIONS

J.W.F. and T.W.K. contributed to all aspects of this paper and agree to be accountable for the content of the work.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. One of us (J.W.F.) has consulted for both food and supplement companies in the past year.

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